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(54) **Delta22-derivatives of LL-F28249 compounds.**

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Description

BACKGROUND OF THE INVENTION

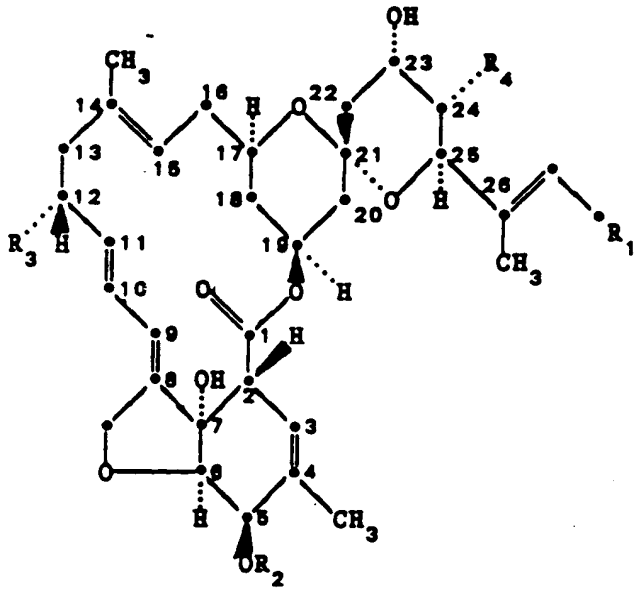
The present invention relates to new derivatives of the antibiotics collectively defined as LL-F28249. These antibiotics preferably are produced by the fermentation of the microorganism Streptomyces cyaneogriseus subsp. noncyanogenus, deposited in NRRL under deposit accession no. 15773.

The present invention further relates to methods and compositions for preventing, treating or controlling helminth, ectoparasite, insect, acarid and nematode infections in warm-blooded animals and agricultural crops by administering thereto prophylactically, therapeutically or pharmaceutically effective amount of the present Δ^{22}-LL-F28249 agents (compounds), mixtures thereof or the pharmaceutically and pharmacologically-acceptable salts thereof.

These infections not only cause devastating effects to animals but also seriously effect the economics of farmers in raising meat-producing animals such as swine, sheep, cattle, goats, rabbits and poultry. Further, such infections are a source of great concern for companion animals such as horses, dogs and cats. Therefore, effective methods for the treatment and prevention of these diseases constantly are being sought.

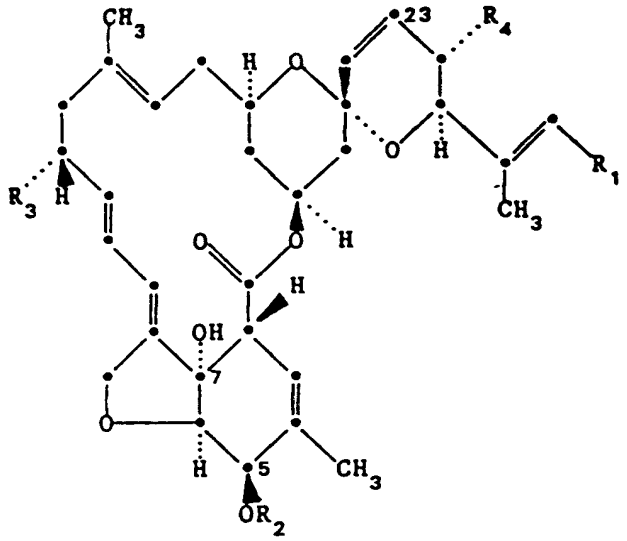
SUMMARY OF THE INVENTION

The present invention provides novel Δ^{22}-derivatives of the compounds designated LL-F28249 and represented by the following structural formula,



Component	R_1	R_2	R_3	R_4
LL-F28249α	$CH(CH_3)_2$	H	CH_3	CH_3
LL-F28249β	CH_3	H	CH_3	CH_3
LL-F28249γ	CH_3	CH_3	CH_3	CH_3
LL-F28249ε	$CH(CH_3)_2$	H	H	CH_3
LL-F28249δ	CH_2CH_3	H	CH_3	CH_3
LL-F28249θ	$CH(CH_3)_2$	H	CH_3	CH_2CH_3
LL-F28249ι	$CH(CH_3)_2$	H	CH_2CH_3	CH_3
LL-F28249λ	$CH(CH_3)_2$	CH_3	CH_3	CH_3

The compounds of the present invention are represented by structural formula (I),



(I)

wherein R_1 is methyl, ethyl or isopropyl; R_2 is hydrogen or methyl; R_3 is hydrogen, methyl or ethyl; R_4 is methyl or ethyl; and the pharmaceutically and pharmacologically acceptable salts thereof.

The compounds of the present invention are useful anthelmintics, ectoparasiticides, insecticides, acaricides and nematicides in treating, preventing or controlling such diseases in warm-blooded animals, such as poultry, cattle, sheep, swine, rabbits, horses, dogs, cats and human beings and agricultural crops.

Although these diseases have been recognized for years and therapies exist for the treatment and prevention of the diseases, the present invention provides novel compounds in the search for effective such therapy.

U.S. Patent 3,950,360, Aoki et al, April 13, 1976, discloses certain antibiotic substances obtained by culturing a Streptomyces microorganism, said compounds being useful as insecticides and acaricides. Further, an entire series of U.S. patents relates to certain compounds produced by the fermentation of Streptomyces avermitilis (EP-A-0 002 615; U.S. Patent 4,171,314, Chabala et al, October 16, 1979; U.S. Patent 4,199,569, Chabala et al, April 22, 1980; U.S. Patent 4,206,205, Mrozik et al, June 3, 1980; U.S. Patent 4,310,519, Albers-Schonberg, January 12, 1982; U.S. Patent 4,333,925, Buhs et al, June 8, 1982). U.S. Patent 4,423,209, Mrozik, December 27, 1983 relates to the process of converting some of these less desirable components to more preferred ones. British Patent Application 2166436A and FR-A-2570309 of Ward et al relates to antibiotics also.

The present compounds or the pharmaceutically and pharmacologically-acceptable salts thereof exhibit excellent and effective treatment and/or prevention of these serious diseases of warm-blooded animals.

It is an object of the present invention, therefore, to provide novel Δ^{22}-compounds of the LL-F28249 series of compounds.

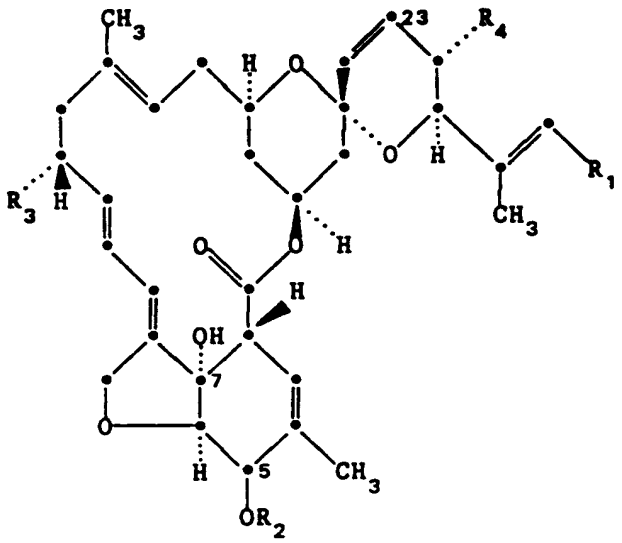
It is a further object of the present invention to provide novel methods for the treatment, prevention or control of helmintic, ectoparasitic, insect, acarid and nematode infections and infestations in warm-blooded animals and agricultural crops.

It also is an object of the present invention to provide novel compositions to effectively control, prevents or treat said diseases in warm-blooded animals.

These and further objects will become apparent by the below-provided detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention are represented by structural formula (I),



(I)

wherein R_1 is methyl, ethyl or isopropyl; R_2 is hydrogen or methyl; R_3 is hydrogen, methyl or ethyl; R_4 is methyl or ethyl; and the pharmaceutically and pharmacologically acceptable salts thereof.

Preferably, R_1 is isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl. Most preferred compound includes R_1 as isopropyl, R_2 as hydrogen, R_3 as methyl and R_4 as methyl.

The Δ^{22}-derivatives of LL-F28249 are prepared by eliminating the 23-hydroxyl group and introducing a double bond at the 22,23 position.

Removal of the 23-hydroxyl group of LL-F28249α, as example of the compounds, is accomplished by initially protecting the 5-hydroxyl group. This protected compound then is derivatized by having the 23-hydroxyl group react with a substituted thiocarbonyl halide, afterwhich the 5-hydroxyl protecting group is removed and 23-oxy group is eliminated to afford the Δ^{22}-LL-F28249α compound.

Suitable protecting groups are trisubstituted silyl groups such as t-butyldimethylsilyl and trimethylsilyl, or trisubstituted silyloxyacetyl groups, such as t-butyldimethylsilycoxy acetyl groups. The protecting groups, however, are not limited to these groups since other useful protecting groups such as acyl and substituted acyl, such as acetyl, trifluoroacetyl, chloroacetyl, trichloroacetyl, phenoxyacetyl and the like, are also useful in the present process.

One of the preferred protecting groups is t-butyldimethylsilyl. This group is attached to the 5-hydroxyl group by reacting an unprotected 5-hydroxy F-28249 compound with t-butyldimethylsilyl chloride in the presence of a base, such as imidazole, pyridine, 4-dimethylaminopyridine, triethylamine and the like, in an aprotic solvent such as methylene chloride, toluene, ethylacetate, tetrahydrofuran, ethylenedichloride and

the like. The reaction is stirred at a temperature of about 0 ° C to 30 ° C, and the reaction is complete in several hours, depending on the temperature of the reaction. The completion of the reaction is usually monitored by high performance liquid chromatography (HPLC) using reverse phase on a Whatman Partisil CCS/C_8 rapid analysis column.

Another preferred protecting group is t-butyldimethylsilyloxy acetyl group. This group is attached to the 5-hydroxyl group by combining the unprotected F-28249 compound in an aprotic solvent such as methylene chloride, toluene, ethyl acetate, tetrahydrofuran, ethylenedichloride and the like, containing a tertiary amine, such as pyridine or triethylamine, and adding the protecting agent in the form of an acid halide. The reaction is conducted at a temperature of about 0 ° C to 30 ° C and is monitored by HPLC for completion.

When the t-butyldimethylsilyloxy acetyl type of protecting group, in the form of an acid halide, is combined with the LL-F28249 compound in an aprotic solvent in the presence of an acid acceptor, as indicated hereinabove, trisubstituted silyl chloride is used. Acid anhydrides also are useful in the present invention instead of the acid chlorides in pyridine containing a catalytic amount of 4-N,N-dimethylaminopyridine.

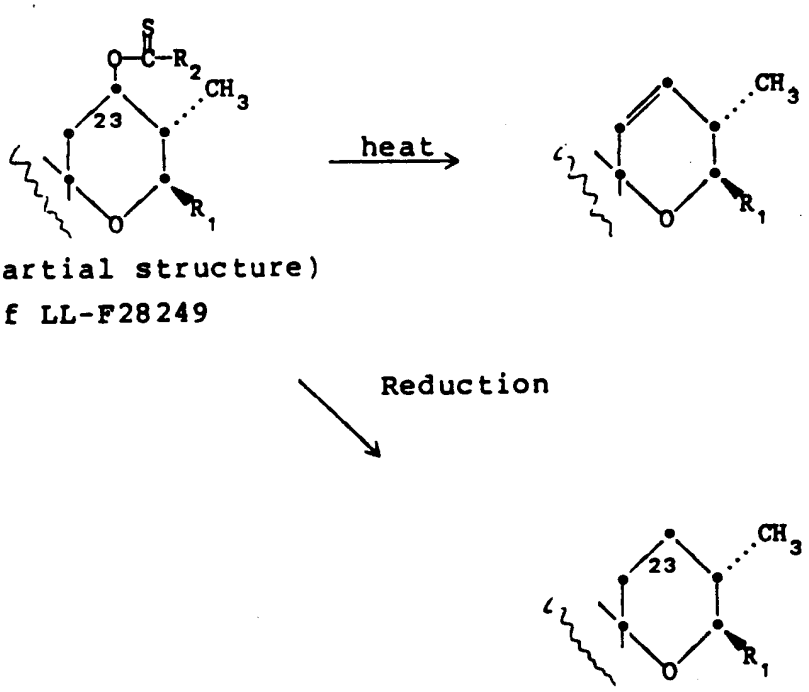
The silyl protecting group is removed by stirring a protected 5-hydroxy F28249 compound in a lower alkanol such as methanol at 0 ° C to room temperature for about 0.5 hour to an hour in the presence of an acid such as p-toluenesulfonic acid. If the protecting group is a silyloxyacetyl group, the silyl group is removed with acid as described above, and the hydroxyacetyl group is cleaved with an equivalent of base such as sodium methoxide in methanol at 0 ° C to toom temperature in 0.5 hour to several hours. The silyloxyacetyl group may also be removed in one step by treatment with sodium methoxide at room temperature until the reaction is complete. Similarly, other acyl protecting groups are removed by base treatment.

With the 5-hydroxyl protected, the 23-hydroxyl group is reacted with a substituted thiocarbonyl halide of the formula:

wherein X is a halogen such as chlorine, bromine or iodine, with chlorine being preferred; and R is a substituted phenoxy, wherein said substitution is a lower alkyl, preferably 4-methyl.

This reaction results in the preparation of a compound with a 23-thiocarbonyloxy group. The reaction is carried out at temperatures of about 0 ° C to 50 ° C for about 0.5-2.0 hours in an aprotic solvent such as methylene chloride, toluene, ethylacetate, tetrahydroguran, ethylenedichloride and the like and a tertiary amine such as pyridine or triethylamine is pyridine and the preferred proton acceptor is 4-dimethylaminopyridine (also functioning as a catalyst). Generally, the thiocarbonyl halide is used in about 10% to 500% molar excess.

The elimination reaction of the tiocarbonyloxy group is carried out in an inert high-boiling solvent such as 1,2-dichlorobenzene or trichlorobenzene at about 150 ° C-225 ° C for about 0.5 to 4.0 hours. The solvent is removed in vacuo, and the product is purified by techniques, such as chromatography known to those skilled in the art. The following schematically illustrates the process.



The thiocarbonyloxy group may also be reduced with reducing agents such as tributyltin hydride in the presence of a free radical initiator such as azobisisobutyronitrile to afford a 23-deoxy-LL-F28249 compound.

Obviously, if the Δ^{22}-LL-F28249 compound wherein R_1 and R_2 are methyl is desired, the starting material is LL-F28249$_\gamma$ and requires no protecting group. Thus, LL-F28249$_\gamma$ is reacted directly with a substituted thiocarbonyl halide, and the resulting product is further processed in the manner described hereinabove to afford Δ^{22}-LL-F28249$_\gamma$.

The compounds of the present invention are useful as anthelmintics, ectoparasiticides, insecticides, acaricides and nematicides.

The disease or group of diseases described generally as helminthiasis is due to infection of an animal host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats and poultry. Among the helminths, the group of worms described as nematodes causes widespread and often times serious infection in various species of animals. The most common genera of nematodes infecting the animals referred to above are Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostomum, Oesophagostomum, Chabertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris and Parascaris. Certain of these, such as Nematodirus, Cooperia, and Oesophagostomum primarily attack the intestinal tract, while others, such as Haemonchus and Ostertagia, are most prevalent in the stomach. Still others, such as Dictyocaulus, are found in the lungs. However, other parasites may be located in other tissues and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs, and, if left untreated, may result in death of the infected host. The LL-F28249 compound derivatives of the present invention unexpectedly have high activity against these parasites. Additionally, the compounds of this invention also are active against Dirofilaria in dogs, Nematospiroides, Syphacia, Aspiculuris in rodents, arthropod ectoparasites such as ticks, mites, lice, fleas, blowfly, of animals and birds, the ectoparasite Lucilia sp. of sheep, biting insects and migrating dipterous larvae such as Hypoderma sp. in cattle, Gastrophilus in horses and Cuterebra sp. in rodents.

The compounds of the present invention also are useful in treating, preventing or controlling parasites (collectively includes ecto and/or endoparasites) which infect human beings, as well. The most common genera of parasites of the gastrointestinal tract of man are Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris, and Enterobius. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filiarial worms such

as Wuchereria, Brugia, Onchocerca and Loa, Dracunculus and extra-intestinal stages of the intestinal worms Strongyloides and Trichinella. The present compounds also are of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

These compounds further are active against household pests such as the cockroach, Blattella sp., clothes moth, Tineola sp., carpet beetle Attagenus sp. and the housefly Musca domestica.

Insect pests of stored grains such as Tribolium sp., Tenebrio sp., and of agricultural plants such as spider mites (Tetranychus sp.), aphids (Acyrthiosiphon sp.), southern army worms, tobacco budworms, boll weevils migratory orthopterans, such as locusts and immature stages of insects living on plant tissue are controlled by the present compounds, as well as the control of soil nematodes and plant parasites such as Meloidogyne sp.

The compounds of the present invention may be administered orally or parenterally for animal and human usage, while they may be formulated in liquid or solid form for agricultural use. Oral administrations may take the form of a unit dosage form such as a capsule, bolus or tablet, or as a liquid drench where used as an anthelmintic for animals.

The animal drench is normally a solution, suspension or dispersion of the active compound, usually in water, together with a suspending agent such as bentonite and a wetting agent or like excipient. Generally, the drenches also contain an antifoaming agent. Drench formulations generally contain about 0.001% to 0.5%, by weight, of the active compound. Preferred drench formulations contain about 0.01% to 0.1% by weight.

Capsules and boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate or di-calcium phosphate.

Where it is desired to administer the Δ^{22}-LL-F28249 derivatives in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the active compound depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the active compounds of the invention may be administered to animals parenterally such as by intraruminal, intramuscular, intratracheal or subcutaneous injection. In such an event, the active compound is dissolved or dispersed in a liquid carrier vehicle.

For parenteral administration, the active compound is suitably admixed with an acceptable vehicle, preferable a vegetable oil such as peanut oil, cotton seed oil or the like. Other parenteral vehicles such as organic preparations using solketal, glycerol formal and aqueous parenteral formulation also are used. The active LL-F28249 compound derivative or derivatives are dissolved or suspended in the parenteral formulation for administration. Such formulations generally contain about 0.005% to 5%, by weight, of the active compound.

Although the compounds of the present invention are primarily used in the treatment, prevention or control of helminthiasis, they also are useful in the prevention, treatment or control of diseases caused by other parasites (collectively both ecto and/or endoparasites). For example, arthropod parasites such as ticks, lice, fleas, mites and other biting insects in domesticated animals and poultry are controlled by the present compounds. These compounds also are effective in treatment of parasitic diseases which occur in other animals including human beings. The optimum amount to be employed will, of course, depend upon the particular compound employed, the species of animal to be treated and the type and severity of parasitic infection or infestation. Generally, the amount useful in oral administration of these novel compounds in about 0.001 mg to 10 mg per kg of animal body weight, such total dose being given at one time or in divided doses over a relatively short period of time (1-5 days). The preferred compounds of the invention give excellent control of such parasites in animals by administering about 0.025 mg to 3 mg per kg of animal body weight in a single dose. Repeat treatments are given as required to combat re-infections and are dependent upon the species of parasite and the husbandry techniques being employed. The techniques for administering these materials to animals are known to those skilled in the veterinary field.

When the compounds described herein are administered as a component of animals' feed or dissolved or suspended in the drinking water, compositions are provided in which the active compound or compounds are intimately dispersed in an inert carrier or diluent. An inert carrier is one that will not react with the active component and that will be administered safely to animals. Preferably, a carrier for feed administration is one that is, or may be, an ingredient of the animal ration.

Suitable compositions include feed premixes or supplements in which the active compound is present in relatively large amounts wherein said feed premixes or supplements are suitable for direct feeding to the animal or for addition to the feed either directly or after an intermediate dilution or blending step.

Typical carriers or diluents suitable for such compositions include distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, wheat shorts, molasses solubles, corn cob meal, edible bean mill feed, soya grits, crushed limestone and the like. The active compounds are intimately dispersed throughout the carrier by methods such as grinding, stirring, milling or tumbling. Compositions containing about 0.005% to 2.0%, by weight, of the active compound are particularly suitable as feed premixes.

Feed supplements, which are fed directly to the animal, contain about 0.0002% to 0.3%, by weight, of the active compounds. Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment and control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular derivative employed, the compounds of this invention are usually fed at concentrations of about 0.00001% to 0.02% in the feed in order to achieve the desired antiparasitic result.

The compounds of this invention also are useful in combating agricultural pests that inflict damage upon growing or stored crops. The present compounds are applied, using known techniques such as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from agricultural pests.

The present invention is illustrated by the following examples which are illustrative of said invention and not limitative thereof.

EXAMPLE 1

5-O-t-Butyldimethlsilyl-LL-F28249α

In 500 mL of CH_2Cl_2, 70 g of LL-F28249α is stirred with 82.04 g of imidazole at 20 °C under N_2 atmosphere. Then, 43 g of t-butyldimethylsilyl chloride in 400 mL of CH_2Cl_2 is added over 5 minutes. After an hour, the reaction is assayed for completion by high performance liquid chromatography (HPLC), using 50% CH_3CN/50% H_2O in a curved gradient mode over 10 minutes on a Whatman C_8-RAC column at 1 mL/min. Another 3 g of t-butyldimethylsilyl chloride is added, and after 3 hours, the composition is 92.3% product, 0.3% LL-F28249α and 1.16% disilylated material. The mixture is diluted with CH_2Cl_2 and poured into 2 L of H_2O. The CH_2Cl_2 layer then is separated. The aqueous portion is extracted with 2 L of CH_2Cl_2, and the combined organic layers are dried (Na_2SO_4). The CH_2Cl_2 is evaporated in vacuo to afford 116 g of the title compound that is identified by mass spectrometry and nuclear magnetic resonance (NMR) spectrometry.

EXAMPLE 2

23-O[(4-Methylphenoxy)thiocarbonyl]-LL-F28249α

In 4 mL of dry pyridine, 291.7 mg of 5-O-t-butyldimethylsilyl-LL-F28249α and 9.7 mg of 4-dimethylaminopyridine are stirred under N_2 atmosphere at 0 °C while 0.62 mL of O-(4-methylphenyl)-chlorothioformate is added dropwise. After the addition is completed, the mixture is stirred at room temperature (about 25 °C) until a solution is obtained. The solution is then heated at 45 °C in an oil bath for 1 hour, cooled and quenched with 1 mL of H_2O at ice bath temperature. The mixture is stirred for 10 minutes at room temperature, diluted with 30 mL of H_2O and extracted with 5 x 15 mL of Et_2O. The combined Et_2O extracts are washed successively with H_2O (2 x 10 mL), $CuSO_4$ solution, H_2O (2 x 10 mL), 10% Na_2CO_3 solution and brine. The ether solution is dried ($MgSO_4$), filtered and evaporated to dryness. The residue is mixed with toluene, evaporated to dryness to remove traces of pyridine and chromatographed over silica gel using 6% EtOAc in hexane. The crude product is dissolved in 3 mL of MeOH containing 30.4 mg of p-toluenesulfonic acid, and the mixture is stirred in an ice bath under N_2 atmosphere for 2 hours. The mixture is then neutralized with $NaHCO_3$ solution, diluted with H_2O and extracted with ether several times. The combined ether extracts are washed with brine and dried ($MgSO_4$) After evaporating to dryness, the residue is chromatographed on silica gel using 5% EtOAc in CH_2Cl_2 containing 5 drops of i-PrOH/100 mL of solvent mixture. Removel of solvents from the desired fractions affords 79.8 mg of the title compound that is characterized by mass spectrometry and NMR spectroscopy.

EXAMPLE 3

Δ^{22}-LL-F28249α

In 1.5 mL of o-dichlorobenzene, 73.4 mg of 23-O[(4-methylphenoxy)thiocarbonyl]-LL-F28249α is heated at reflux temperature under N_2 atmosphere for 3 hours. The solution is cooled. The solvent then is removed in vacuo, and the residue is chromatographed on silica gel using 7% EtOAc in CH_2Cl_2 containing 10 drops of i-PrOH per 100 mL of solvent mixture. Evaporation of the solvents from the desired fraction affords 28.4 mg of the title compound that is characterized by mass spectrometry and NMR spectroscopy.

EXAMPLES 4 AND 5

23-O[(4-Methylphenoxy)thiocarbonyl]-LL-F28249γ

Following the procedure of Example 2, LL-F28249γ is reacted with O-(4-methylphenyl)chlorothioformate to afford the title compound that is identified by mass spectrometry and NMR spectroscopy.

Similarly, O[(4-methylphenoxy)thiocarbonyl]-LL-F28249λ is prepared.

EXAMPLES 6 AND 7

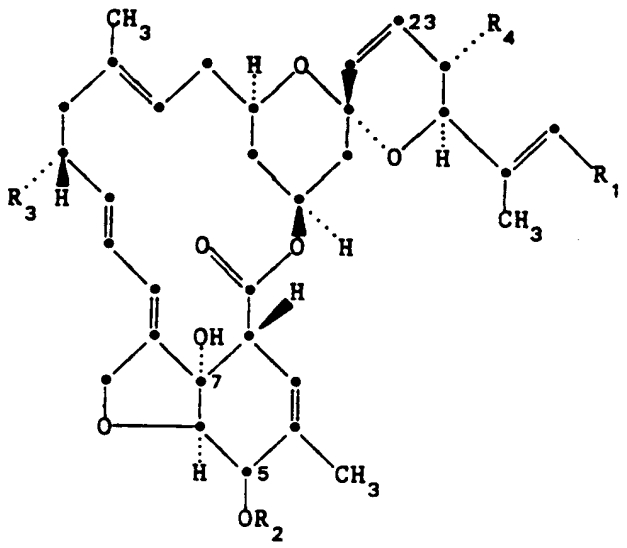
Δ^{22}-LL-F28249γ

By the procedure of Example 3, the title compound is prepared from 23-O[(4-methylphenoxy)-thiocarbonyl]-LL-F28249γ. The title compound is identified by mass spectrometry and NMR spectroscopy.

Similarly, Δ^{22}-LL-F28249λ is prepared by this procedure.

EXAMPLES 8-12

Using the method of Example 1 to protect the 5-hydroxy group, followed by derivatization of the 23-hydroxy group by the method of Example 2 and decomposing the 23-O[(4-methylphenoxy)thiocarbonyl]-LL-F28249 compounds by the method of Example 3, the following commpounds are prepared:



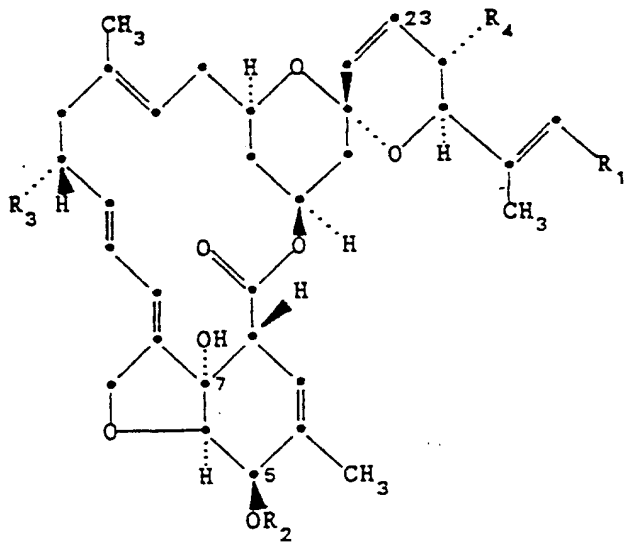
(I)

R_1	R_2	R_3	R_4
CH_3	H	CH_3	CH_3
$CH_3(CH_3)_2$	H	H	CH_3
CH_2CH_3	H	CH_3	CH_3
$CH(CH_3)_2$	H	CH_3	CH_2CH_3
$CH(CH_3)_2$	H	CH_2CH_3	CH_3

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The compounds characterized by structural formula (I),



(I)

wherein R_1 is methyl, ethyl or isopropyl; R_2 is hydrogen or methyl; R_3 is hydrogen, methyl or ethyl; R_4 is methyl or ethyl; and the pharmaceutically and pharmacologically acceptable salts thereof.

2. A compound according to Claim 1, wherein R_1 is isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl; and wherein R_1 is isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

3. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the prevention, treatment or control of parasitic infections in warm-blooded animals, by orally, topically or parenterally administering to an animal infected with parasites, a parasiticidally-effective amount of the compounds represented by structural formula (I); or the pharmaceutically and pharmacologically acceptable salts thereof.

4. A use according to Claim 3, wherein said compound has R_1 as isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 as methyl; and wherein said compound has R_1 as isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

5. A method for controlling plant insects, topically or systemically, and protecting crops, trees, shrubs, stored grain and ornamentals, said method characterized by: applying an insecticidally-effective amount

of the compound represented by the structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof.

6. A method according to Claim 5, wherein said compound is applied to the foliage of crops and plants the soil in which they are grown or the trunk thereof.

7. A method according to Claim 6, wherein said compound has R_1 as isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl; and wherein said compound is R_1 as isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

8. A method for the control of plant nematodes, said method characterized by: applying to the foliage of plants, the soil in which they are grown or into the trunks thereof, a nematocidally-effective amount of the compound represented by structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof.

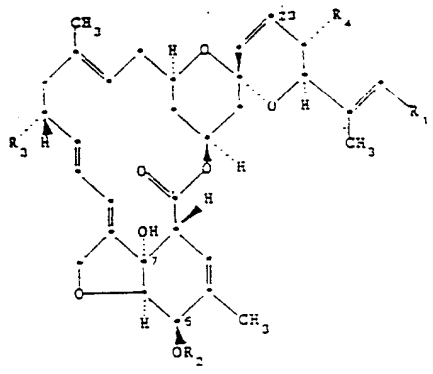
9. A method according to Claim 8, wherein said compound has R_1 as isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl; and wherein said compound has R_1 as isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

10. A composition for the treatment, prevention or control of parasitic infections in warm-blooded animals, said composition characterized by: a prophylactically, therapeutically or pharmaceutically-effective amount of the compound represented by structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof; and an inert carrier.

11. A composition for controlling plant insects, said composition characterized by: an insecticidally-effective amount of the compound represented by structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof; and an inert carrier.

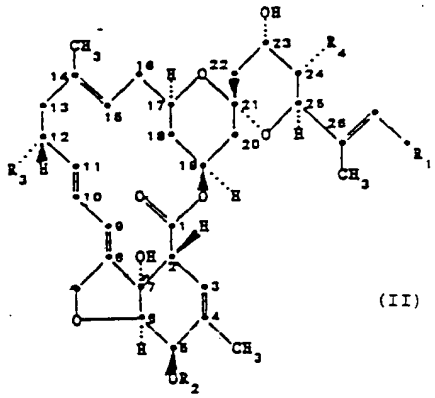
Claims for the following Contracting States : AT, ES, GR

1. A process for producing compounds of structural formula (I)



(I)

wherein R_1 is methyl, ethyl or isopropyl; R_2 is hydrogen or methyl; R_3 is hydrogen, methyl or ethyl; R_4 is methyl or ethyl; and the pharmaceutically and pharmacologically acceptable salts thereof; said process characterized by: protecting the 5-hydroxyl group on structural formula (II)



(II)

with a protecting agent; derivatizing the 23-hydroxyl group with a substituted thiocarbonyl halide; deprotecting the 5-hydroxyl group and removing the 23-oxy group.

2. The process according to Claim 1, wherein the protecting groups are trisubstituted silyl groups, trisubstituted silyloxyacetyl groups, acyl and substituted acyl groups.

3. A method for controlling plant insects, topically or systemically, and protecting crops, trees, shrubs, stored grain and ornamentals, said method characterized by: applying an insecticidally-effective amount of the compound represented by the structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof.

4. A method according to Claim 3, wherein said compound is applied to the foliage of crops and plants the soil in which they are grown or the trunk thereof.

5. A method according to Claim 4, wherein said compound has R_1 as isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl; and wherein said compound is R_1 as isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

6. A method for the control of plant nematodes, said method characterized by: applying to the foliage of plants, the soil in which they are grown or into the trunks thereof, a nematocidally-effective amount of the compound represented by structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof.

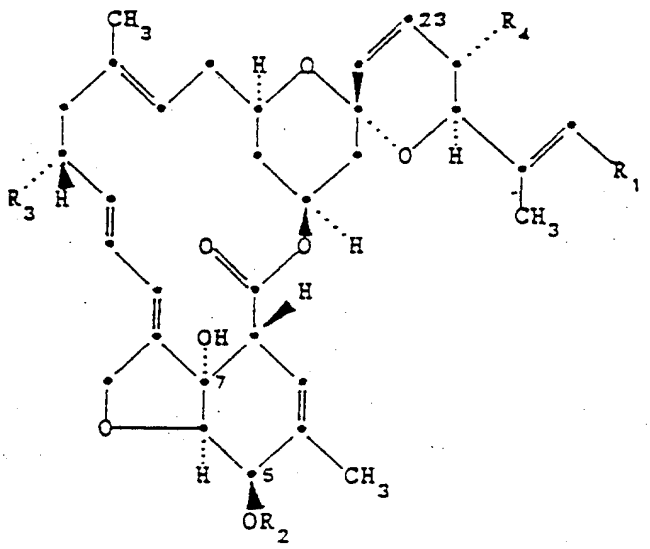
7. A method according to Claim 6, wherein said compound has R_1 as isopropyl; R_2 is hydrogen or methyl; R_3 is methyl; and R_4 is methyl; and wherein said compound has R_1 as isopropyl; R_2 is hydrogen; R_3 is methyl; and R_4 is methyl.

8. A composition for controlling plant insects, said composition characterized by: an insecticidally-effective amount of the compound represented by structural formula (I), as defined in Claim 1; or the pharmaceutically and pharmacologically acceptable salts thereof; and an inert carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Die Verbindungen, die durch die Strukturformel (I) charakterisiert sind



(I)

worin R_1 Methyl, Ethyl oder Isopropyl ist; R_2 Wasserstoff oder Methyl ist; R_3 Wasserstoff, Methyl oder Ethyl ist; R_4 Methyl oder Ethyl ist, und deren pharmazeutisch und pharmakologisch akzeptable Salze:

2. Eine Verbindung nach Anspruch 1, worin R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

3. Verwendung einer Verbindung, wie sie in Anspruch 1 definiert ist, zur Herstellung eines Medikaments zur Verhinderung, Behandlung oder Bekämpfung parasitärer Infektionen in warmblütigen Tieren durch orales, örtliches oder parenterales Verabreichen an ein Tier, das mit Parasiten infiziert ist, von einer parasitizid wirksamen Menge der Verbindungen, die durch die Strukturformel (I) repräsentiert sind oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen.

4. Eine Verwendung nach Anspruch 3, worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

5. Ein Verfahren zum örtlichen oder systematischen Bekämpfen von Pflanzeninsekten und zum Schützen von Feldfrüchten, Bäumen, Sträuchern, gelagertem Getreide und Zierpflanzen, wobei das Verfahren charakterisiert ist durch Anwenden einer insektizid wirksamen Menge der Verbindung, die durch die Strukturformel (I) repräsentiert ist, wie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen.

6. Ein Verfahren nach Anspruch 5, worin die Verbindung auf das Laub der Feldfrüchte und Pflanzen, den Boden, in dem sie wachsen oder deren Stamm aufgebracht wird.

7. Ein Verfahren nach Anspruch 6, worin in der Verbindung R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

8. Ein Verfahren zum Bekämpfen von Pflanzennematoden, wobei das Verfahren charakterisiert ist durch Anwenden einer nematozid wirksamen Menge der Verbindung der Strukturformel (I), wie sie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen auf das Laub der Pflanzen, den Boden in dem sie wachsen oder deren Stämme.

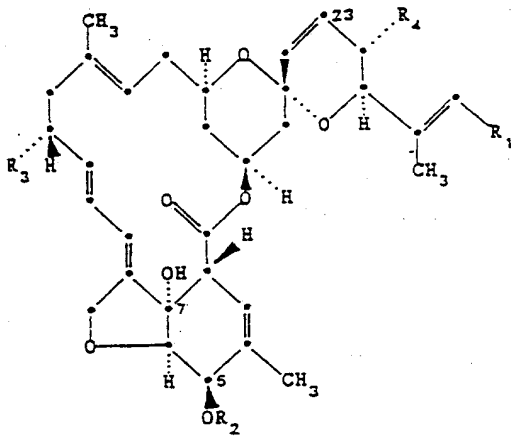
9. Ein Verfahren nach Anspruch 8, worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

10. Eine Zusammensetzung zur Behandlung, Verhinderung oder Bekämpfung parasitärer Infektionen in warmblütigen Tieren, wobei die Zusammensetzung charakterisiert ist durch eine prophylaktisch, therapeutisch oder pharamzeutisch wirksame Menge der Verbindung der Strukturformel (I), wie sie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen, sowie einen inerten Träger.

11. Eine Zusammensetzung zum Bekämpfen von Pflanzeninsekten, wobei die Zusammensetzung charakterisiert ist durch eine insektizid wirksame Menge der Verbindung der Strukturformel (I), wie sie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen sowie einen inerten Träger.

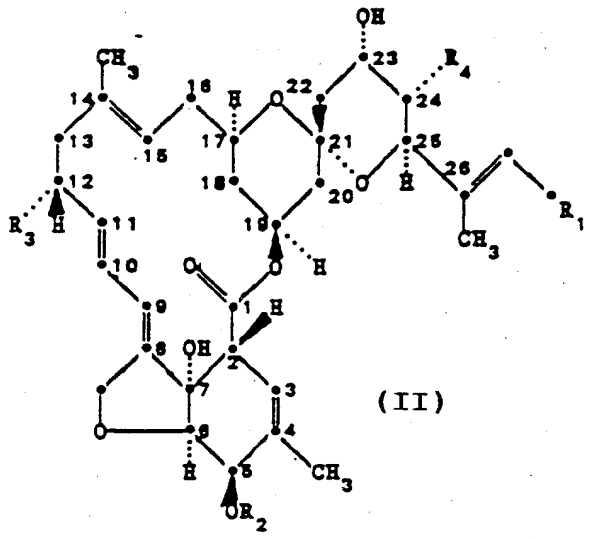
Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Ein Verfahren zum Herstellen von Verbindungen der Strukturformel (I)



(I)

worin R_1 Methyl, Ethyl oder Isopropyl ist; R_2 Wasserstoff oder Methyl ist; R_3 Wasserstoff, Methyl oder Ethyl ist; R_4 Methyl oder Ethyl ist, und deren pharmazeutisch und pharmakologisch akzeptable Salze wobei das Verfahren charakterisiert ist durch:
Schützen der 5-Hydroxylgruppe bei der Strukturformel (II)



(II)

mit einem Schutzmittel, Herstellen eines Derivats der 23- Hydroxylgruppe mit einem substituierten Thiocarbonylhalogenid, Abspalten der Schutzgruppe von der 5-Hydroxylgruppe und Entfernen der 23-Oxygruppe.

2. Das Verfahren nach Anspruch 1, worin die Schutzgruppen trisubstituierte Silylgruppen, trisubstituierte Silyloxyacetylgruppen und substituierte Acylgruppen sind.

3. Ein Verfahren zum örtlichen oder systematischen Bekämpfen von Pflanzeninsekten und zum Schützen von Feldfrüchten, Bäumen, Sträuchern, gelagertem Getreide und Zierpflanzen, wobei das Verfahren charakterisiert ist durch Anwenden einer insektizid wirksamen Menge der Verbindung, die durch die Strukturformel (I) repräsentiert ist, wie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen.

4. Ein Verfahren nach Anspruch 3, worin die Verbindung auf das Laub der Feldfrüchte und Pflanzen, den Boden, in dem sie wachsen oder deren Stamm aufgebracht wird.

5. Ein Verfahren nach Anspruch 4, worin in der Verbindung R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

6. Ein Verfahren zum Bekämpfen von Pflanzennematoden, wobei das Verfahren charakterisiert ist durch Anwenden einer nematozid wirksamen Menge der Verbindung der Strukturformel (I), wie sie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen auf das Laub der Pflanzen, den Boden in dem sie wachsen oder deren Stämme.

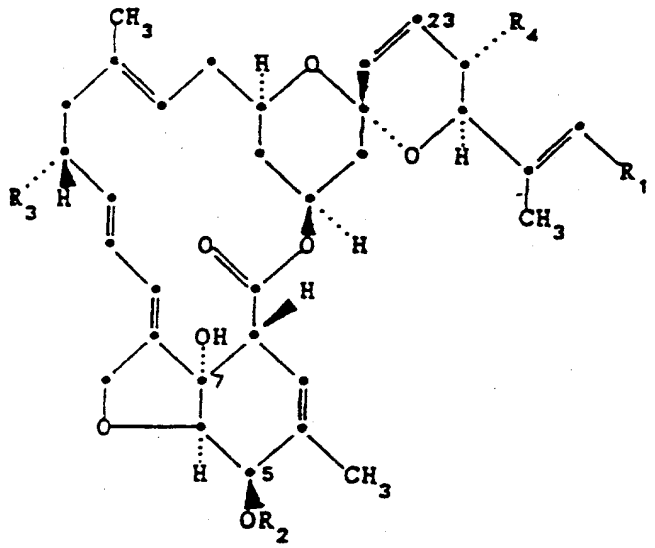
7. Ein Verfahren nach Anspruch 6, worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff oder Methyl, R_3 Methyl und R_4 Methyl ist und worin bei der Verbindung R_1 Isopropyl, R_2 Wasserstoff, R_3 Methyl und R_4 Methyl ist.

8. Eine Zusammensetzung zum Bekämpfen von Pflanzeninsekten, wobei die Zusammensetzung charakterisiert ist durch eine insektizid wirksame Menge der Verbindung der Strukturformel (I), wie sie in Anspruch 1 definiert ist oder von deren pharmazeutisch und pharmakologisch akzeptablen Salzen sowie einen inerten Träger.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés caractérisés par la formule développée (I)



(I)

dans laquelle R_1 est un méthyle, un éthyle ou un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est l'hydrogène, un méthyle ou un éthyle; R_4 est un méthyle ou un éthyle; et leurs sels pharmaceutiquement et pharmacologiquement acceptables.

2. Composé selon la revendication 1, dans lequel R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans lequel R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

3. Utilisation d'un, composé tel que défini dans la revendication 1 pour la fabrication d'un médicament pour la prévention, le traitement ou la maîtrise d'infections parasitaires chez les animaux à sang chaud, par administration orale, topique ou parentérale, à un animal infecté par des parasites, d'une quantité efficace comme parasiticide des composés représentés par la formule développée (I) ou de leurs sels pharmaceutiquement et pharmacologiquement acceptables.

4. Utilisation selon la revendication 3, dans laquelle, dans ledit composé, R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans laquelle, dans ledit composé, R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

5. Méthode pour maîtriser les insectes des végétaux, de façon topique ou systémique, et pour protéger les récoltes, les arbres, les arbustes, les grains emmagasinés et les plantes ornementales, ladite méthode étant caractérisée par l'application d'une quantité efficace comme insecticide du composé représenté par la formule développée (I), telle que définie dans la revendication 1, ou de ses sels pharmaceutiquement et pharmacologiquement acceptables.

6. Méthode selon la revendication 5, dans laquelle ledit composé est appliqué sur le feuillage des cultures et des plantes, sur le sol dans lequel elles sont cultivées ou sur leur tronc.

7. Méthode selon la revendication 6, dans laquelle, dans ledit composé, R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans laquelle, dans ledit composé, R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

8. Méthode pour maîtriser les nématodes des végétaux, ladite méthode étant caractérisée par l'application sur le feuillage de végétaux, sur le sol dans lequel ils sont cultivés ou dans leurs troncs d'une quantité efficace comme nématocide du composé représenté par la formule développée (I) telle que définie dans la revendication 1, ou de ses sels pharmaceutiquement et pharmacologiquement acceptables.

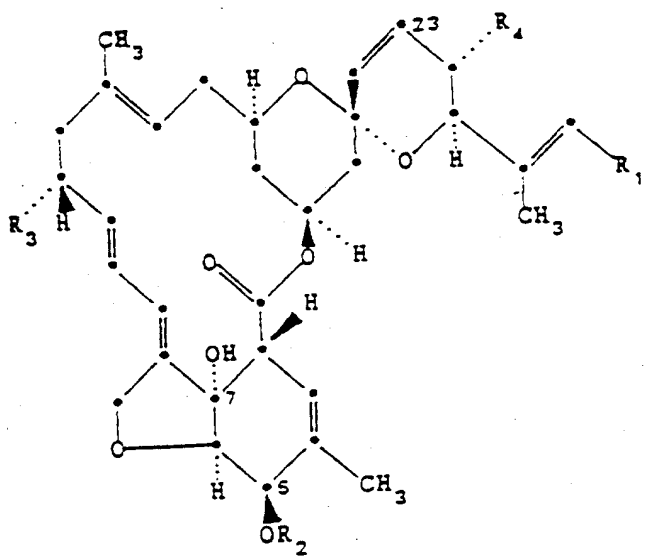
9. Méthode selon la revendication 8, dans laquelle, dans ledit composé, R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans laquelle, dans ledit composé, R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

10. Composition pour le traitement, la prévention ou la maîtrise d'infections parasitaires chez les animaux à sang chaud, ladite composition étant caractérisée par une quantité prophylactiquement, thérapeutiquement ou pharmaceutiquement efficace du composé représenté par la formule développée (I) telle que définie dans la revendication 1 ou de ses sels pharmaceutiquement et pharmacologiquement acceptables; et par un support inerte.

11. Composition pour la maîtrise des insectes des végétaux, ladite composition étant caractérisée par une quantité efficace comme insecticide du composé représenté par la formule développée (I) telle que définie dans la revendication 1 ou de ses sels pharmaceutiquement et pharmacologiquement acceptables; et par un support inerte.

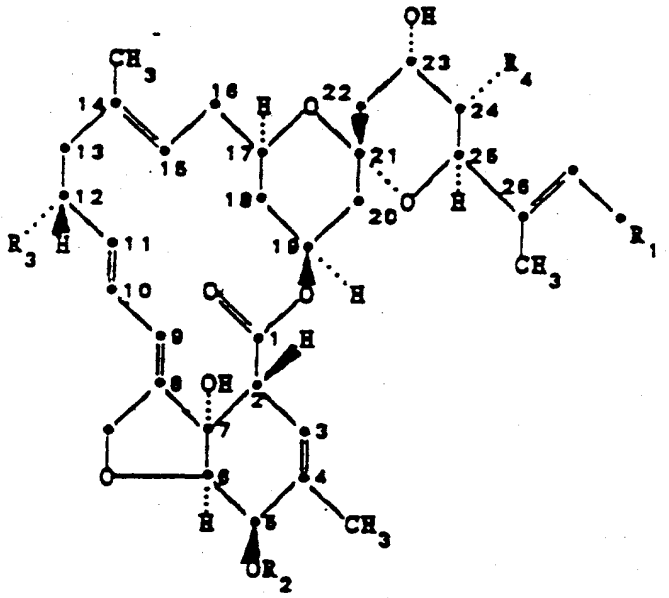
Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé de production de composés ayant la formule développée (I)



(I)

dans laquelle R_1 est un méthyle, un éthyle ou un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est l'hydrogène, un méthyle ou un éthyle; R_4 est un méthyle ou un éthyle; et de leurs sels pharmaceutiquement et pharmacologiquement acceptables, ledit procédé étant caractérisé par la protection du groupe 5-hydroxyle dans la formule développée (II)



avec un agent protecteur; la formation d'un dérivé du groupe 23-hydroxyle avec un halogénure de thiocarbonyle substitué; la libération du groupe 5-hydroxyle et l'élimination du groupe 23-oxy.

2. Procédé selon la revendication 1, dans lequel les groupes protecteurs sont des groupes silyle trisubstitués, des groupes silyloxyacétyle trisubstitués, des groupes acyle et des groupes acyle substitués.

3. Méthode pour maîtriser les insectes des végétaux, de façon topique ou systémique, et pour protéger les récoltes, les arbres, les arbustes, les grains emmagasinés et les plantes ornementales, ladite méthode étant caractérisée par l'application d'une quantité efficace comme insecticide du composé représenté par la formule développée (I), telle que définie dans la revendication 1, ou de ses sels pharmaceutiquement et pharmacologiquement acceptables.

4. Méthode selon la revendication 3, dans laquelle ledit composé est appliqué sur le feuillage des cultures et des plantes, sur le sol dans lequel elles sont cultivées ou sur leur tronc.

5. Méthode selon la revendication 4, dans laquelle, dans ledit composé, R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans laquelle, dans ledit composé, R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

6. Méthode pour maîtriser les nématodes des végétaux, ladite méthode étant caractérisée par l'application sur le feuillage de végétaux, sur le sol dans lequel ils sont cultivés ou dans leurs troncs d'une quantité efficace comme nématocide du composé représenté par la formule développée (I) telle que définie dans la revendication 1, ou de ses sels pharmaceutiquement et pharmacologiquement acceptables.

7. Méthode selon la revendication 6, dans laquelle, dans ledit composé, R_1 est un isopropyle; R_2 est l'hydrogène ou un méthyle; R_3 est un méthyle; et R_4 est un méthyle; et dans laquelle, dans ledit composé, R_1 est un isopropyle, R_2 est l'hydrogène, R_3 est un méthyle et R_4 est un méthyle.

8. Composition pour le traitement, la prévention ou la maîtrise d'infections parasitaires chez les animaux à sang chaud, ladite composition étant caractérisée par une quantité prophylactiquement, thérapeutiquement ou pharmaceutiquement efficace du composé représenté par la formule développée (I) telle que définie dans la revendication 1 ou de ses sels pharmaceutiquement et pharmacologiquement acceptables; et par un support inerte.